0031-3998/04/5602-0165
PEDIATRIC RESEARCH

Vol. 56, No. 2, 2004
Printed in U.S.A.

RESEARCH NEWS

Research in Children: Assessing Risks and Benefits

A review of: Shah S, Whittle A, Wilfond B, Gensler G, Wendler D 2004 How do Institutional Review Boards apply the Federal Risk and Benefit Standards for pediatric research? JAMA 291:476–482

STANLEY G. KORENMAN

THE PRINCIPLE OF justice indicates that the category of persons for whom a treatment is proposed should share equally in both the privilege and responsibility of participating in the research evaluating such treatments. The past twenty years have seen great advances in the diversification of research participation to involve minorities, women of childbearing age, those over 70, and the cognitively impaired. Children and pregnant women constitute the main vulnerable populations in which participation remains limited. Children differ from most other research participants in that they themselves do not consent but that responsibility is given to their parents or guardians. Even those older children assenting to participation are often considered to have a limited understanding of the research process.

Wary of making decisions for others, the poor understanding of both their guardians and researchers of the true risks and benefits involved in clinical investigation may be a major reason for the lackluster participation of children in research. That is remediable by empirical study.

Recognizing the need to understand the dosing, efficacy and safety of drugs used to treat children, the Federal Government issued regulations that hopefully empowered Institutional Review Boards (IRBs) to approve studies in children in 4 risk categories as delineated in "the Common Rule," Federal Regulation 45CFR46 sections 404–7.

- Research that involves no greater than minimal risk to children.
- Research that involves greater than minimal risk, but the risk is justified by the anticipated benefit to the participants and the relation of the anticipated benefits to the risk is at least as favorable as that presented by alternative approaches.
- Research that involves greater than minimal risk and no prospect of direct benefit to research participants but (a) the risk represents only a minor increase over minimal risk, (b) the research involves experience reasonably commensurate with those inherent in the child's medical, dental, psychological, social or educational situation, and (c) the research is likely to yield generalizable, vitally important knowledge about a child's disorder or condition.
- Research that is not otherwise approvable, but that the IRB and the Secretary of DHHS (through a panel of experts) determine presents an opportunity to understand, prevent, or alleviate a serious problem affecting children's health or welfare and will be conducted in accordance with sound ethical principles.

Minimal risk has been defined as the "risk of harm or discomfort ordinarily encountered in daily life or during the performance of routine medical or psychological examinations." It was left to the individual IRBs, when confronted with a protocol, to determine whether the criteria of "benefit", "minimal risk," or "minor increase" were met. Variable interpretations of those terms might have been expected. In American society, where enormous effort is often expended to protect children from the risks of everyday life, it might have been expected that the line of permissibility would be drawn very strictly.

The issues surrounding pediatric participation in research were addressed in a recent JAMA article (1). Shah et al. reported on the basis of communicating with 188 randomly selected IRB Chairs, that even benign interventions including MRIs without contrast, allergy skin testing, and a confidential survey of sexual activity in teens were not considered minimal risk by a majority of respondents. A pharmacological study with a risk of death of 1 in 100,000 was considered to be more than a minor increase over minimal risk by the majority of IRB chairs, making it impossible to carry out such a study unless there was a viable claim for a positive risk to benefit ratio, *i.e.* a significant possible benefit. On the other hand, 37% of IRB chairs saw such a study as presenting minimal risk. These hypothetical perceptions were not evidence-based. In real protocols presented to the IRB, the true risks and benefits are always speculative until the study is complete but empirical estimates can be made about the risk of medical procedures employed during the research. The authors also indicate that while psychological risks are well represented in the equation, psychological benefits are not routinely considered.

The Academy of Medicine recently concluded a two-year study of research involving children (2). Among their many conclusions and recommendations was a call for more empirical studies of risk and for the DHHS OHRP (Office of Human Research Protection) to commission reports to help IRBs determine risks and benefits and thus estimate the risk/benefit ratio.

As noted in the IOM report, "Despite these advances, pediatricians and oth-

ers have argued that infants, children, and adolescents have not shared equally with adults in advances in biomedicine. In particular, many drugs with potential pediatric uses have not been tested in studies that include children. These drugs may still be prescribed for children . . .Because children differ physiologically from adults in myriad ways . . . extrapolation based on adult drug doses and children's weight or age can be dangerous and lead to underdosing, overdosing, or specific adverse effects not evident in adults" (2).

I believe that the professional pediatrics community should undertake an ongoing program of assessing risk of common research interventions by age and publish these for the benefit of pediatric investigators and IRBs, which, except in children's hospitals, are not composed primarily of people who care professionally for children. We need not only more uniformity but also a more cogent assessment of appropriate risks to ask children and their parents to accept in the effort to improve the medical and psychological treatment of children.

REFERENCES

1. Shah S, Whittle A, Wilfond B, Gensler G, Wendler D 2004 How do Institutional Review Boards apply the Federal Risk and Benefit Standards for pediatric research? JAMA 291:476–482
2. Committee on Clinical Research Involving Children 2004 The Ethical Conduct of Clinical Research Involving Children. The National Academies Press, Washington, D.C.

Associate Dean for Ethics and
Professor of Medicine
David Geffen School of Medicine at UCLA
10833 Le Conte Avenue
Los Angeles, CA 90095
E-mail: skorenman@mednet.ucla.edu

DOI: 10.1203/01.PDR.0000135979.26187.86